- Adopting ventilation control systems including filters, fans, or other air-blowing equipment to prevent odors or vapors;
- Additional lighting to ensure that equipment, contact surfaces, or other areas where supplements are examined, processed, or held can be adequately seen.

Sanitation also requires that equipment utensils must be of suitable design, construction, and workmanship to enable them to be adequately cleaned and maintained. To meet this requirement, some establishments may need to provide additional maintenance or additional cleaning and sanitation for their equipment and utensils. Also, freezers and cold storage compartments used to slow or arrest the growth of microorganisms must be fitted with thermometers to accurately show the temperature within the compartments. Instruments and devices used in manufacturing must be accurate, adequately maintained, and adequate in number. To meet this requirement establishments might have to purchase new equipment, replace old equipment, or provide additional maintenance to existing equipment.

ii. Production and process controls. Production and process controls are the main preventive mechanism to ensure the identity, purity, quality, strength, and composition in the proposed rule. Establishments must implement a system of production and process controls that covers all stages of

processing, from the receipt and acceptance of components, dietary ingredients, dietary supplements, packaging, and labels through the release for distribution and holding of the dietary ingredients and dietary supplements. Establishments must identify points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration. Establishments must also establish specifications for the identity, quality, purity, strength, and composition of components, dietary ingredients, or dietary supplements. Establishments must monitor the points, steps, or stages in the batch production, as specified in the master manufacturing record, where control is necessary to prevent adulteration. Establishments must establish specifications for packaging to ensure that containers or closures that come into contact with dietary ingredients or dietary supplements are not reactive or absorptive and are composed of substances that are safe for use in or on food.

Establishments that have not already done so must establish a quality control unit with one or more individuals that have with the authority and responsibility to review the results of monitoring, make decisions on the disposition of materials, and identify whether actions taken to correct any deviations are appropriate. The quality control operation must ensure that

components, dietary ingredients, and dietary supplements conform to specifications.

iii. Holding and distributing. Establishments must hold and distribute dietary ingredients and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, quality, purity, strength, and composition of the dietary ingredients and dietary supplements are not affected. Establishments must also identify and hold components, in-process materials, and dietary supplements under conditions that will protect them against mixups and physical, chemical, and microbial contamination. Packaging materials must also be protected against deterioration. Establishments that do not now perform these requirements and the other provisions associated with holding will incur a compliance cost.

iv. Consumer complaints. The quality control unit must review all consumer complaints involving the failure of a dietary supplement to meet any of its specifications, or the failure to meet any other requirements under proposed part 111, including those specifications and other requirements that, if not met, may result in possible illness or injury. In addition, the quality control unit must investigate such a consumer complaint where there is a reasonable possibility of a relationship between the consumption of a dietary supplement and an adverse event. The complaint and report of the investigation results should be

reported to FDA when there is a possibility of a serious adverse event.

c. Major costs by type of activity. Within these four categories (sanitation, production and process controls, holding and distributing, consumer complaints), the major costs of the proposed rule are recordkeeping (except for sanitation), capital costs for physical plant and equipment, finished product quality testing (part of production and process controls only), labor costs for certain required tasks, and some other costs that were not easily classified.

i. Recordkeeping. We used a study of a medical device CGMP regulation to estimate the costs of recordkeeping (Ref. E44). We request comments on the applicability of a study of the medical device CGMP's to dietary supplements.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use mandatory records is a recurring cost that depends on how frequently records are modified, the frequency of personnel turnover, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate, which we assumed is $15.65 per hour based on the average manufacturing wage, multiplied by the expected labor hours necessary to perform a written or electronic record

and the time necessary for management to review the records to see the actions are documented accurately. For electronic records, the recurring time is the time necessary to ensure that the equipment is serviced and maintained properly.

ii. Capital costs for physical plant and equipment. We estimated capital costs for physical plant redesign at $50 per square foot (Ref. E45). For establishments with inadequate facilities, we assumed that between 0 and 20 percent of the physical plant would have to be renovated, with 10 percent the most likely. For equipment costs, we assumed that very small establishments would on average spend 0 to $1,000, with $100 the most likely amount. Small establishments would bear costs 3 times that of very small establishments, which is the ratio of the size of the physical plants of small establishments to the size of the physical plants of very small establishments. We assumed that large establishments would bear (if necessary) costs 20 times that of very small establishments, which is the ratio of the size of the physical plants of large establishments to the size of the physical plants of very small establishments. In other words, we assumed capital costs for physical plant and equipment would be proportional to facility size, as measured in square feet.

iii. Testing. Establishments that do not already conduct the required product quality tests of each batch of dietary

ingredients or dietary supplement produced would incur the cost for those tests. Under the option for more restrictive CGMP rules, each lot of components would also be tested. The costs per establishment depend on both the number of tests and the costs per test. We did not estimate the cost of developing new, validated tests methods because we lacked information about the costs for this requirement and the number of such tests that need to be developed. We ask for comments on the costs to develop tests, for the number of tests and the costs for performing each test to comply with this requirement.

- Number of tests: Model

To estimate the costs of testing, we first estimated the number and costs of individual tests, without adjusting for the amount of testing already being done. In this section we show how we estimated the likely number of required tests, unadjusted for current voluntary testing. For a representative manufacturer, the annual number of tests would be the number of new tests per batch multiplied by the number of batches produced in a year.

The proposed rule requires only tests for identity, purity, quality, strength, and composition of the final product. The option for stricter CGMP regulations would also require tests of components. Estimating the number of component tests per batch is complicated, because component tests are made on the shipment

lots, rather than on the parts of the lots that actually go into the final product. For example, if a lot of some ingredient is used in 6 batches of final products, it would probably be tested only once.

The establishment itself may test the shipment lots, and during inprocess stages for identity, purity, quality, strength, and composition, unless final product testing is done.

The number of component tests per batch of final product would equal the number of tests per component, multiplied by the number of components per batch, divided by the batches per shipment lot (to account for the production of multiple batches of dietary supplements from single lots of components).

The option for stricter CGMP regulations options would also require some inprocess tests upon receipt. The number of inprocess tests per batch is the same as the number of potential inprocess product defects. The estimated number of inprocess tests counts only tests for defects that can occur during production, not tests for the defects of dietary ingredients and components supplied to the producer.

We used the following formulas to estimate the number of tests:

Component test per batch = $[\sum_{m_j} (I_j \times R_j) + \sum^{n}_{k} (U_k \times R_k)] \times (S / B)$

Inprocess quality tests per batch = $\sum^{\circ}_{1} (H_1 \times R_1)$

Quality tests per batch of final product = max [m x (1/z), 1]

where:

I_j = jth listed ingredient;

m = number of ingredients per batch;

R_j = required tests for ingredient j;

U_k = kth unlisted component (an inactive substance);

n = number of unlisted components per batch;

R_k = required tests for unlisted component k;

S = number of shipments (or lots) of ingredients and unlisted components;

B = number of batches produced;

H_l = lth inprocess potential defects;

R_l = required inprocess tests per batch for potential defect H_l;

o = number of potential inprocess defects per batch;

z = number of ingredients identified per quality test.

- Number of tests: Evidence and distributions

The quantity and quality of evidence on the variables used to estimate the number of required tests varies greatly. In this section, we explain the evidence and assumptions we used to construct the formulas for the number of tests.

- Number of ingredients

We based our measure of the number of dietary ingredients per product on a sample of almost 3,000 dietary supplement labels (Ref. E46). Although some dietary ingredients may be missing from the labels and some listed dietary ingredients may be missing from the products, the ingredient list represents the best evidence we are likely to have on what dietary ingredients are used in dietary supplements.

- Number of ingredients per batch

According to the sample of listed ingredients (Ref. E46). Vitamin and mineral products contain about 13 listed ingredients. Other dietary supplements, mainly herbals, contain about four.

- Number of tests per ingredient lot

The option for more restrictive CGMP regulations would require that virtually all dietary ingredients be tested for identity and defects at some stage between harvesting the raw product and the beginning of the production of the final product. We assumed one identity test per ingredient lot. The number of tests for defects depends on the number of possible defects, which can include:

Filth;

Microbial pathogens;

Chemical hazards, including pesticides;

Insects;

Physical hazards, such as metals;

Natural toxins, such as aflatoxin; and

Inadequate purity, quality, strength, or composition.

The number of potential defects is potentially unlimited. As a practical maximum, however, few products would have more than five potential defects. In the calculation of ingredient testing costs (part of the option for more restrictive CGMP regulations), we assumed that the average number of tests per listed dietary ingredient would be between one and six: One identity test for identity, purity, strength, quality, and composition and zero to five tests for defects.

- Number of unlisted components

Dietary supplements are manufactured using solvents, binders, and lubricants that may not show up in the final product. An industry source (Ref. E47) says that four to six unlisted components are typical per product, although fewer are certainly possible. The minimum number is zero. We assumed that the number of unlisted components would be zero to six, with four the most likely.

- Number of tests per unlisted components

The unlisted components tend to be manufactured products, such as solvents. Therefore, one identity test would likely be sufficient.

- Number of shipments (or lots) of ingredients and unlisted components

We have no direct evidence on the number of shipment lots of dietary ingredients and components. We also have no evidence on the number of shipments per lot or on the number of shipments per batch. The increasing use of just-in-time inventory practices indicates that one shipment lot of components per batch may be the rule for some products and some producers. It is costly and difficult to store ingredients for an extended time, so establishments tend to buy more and smaller lots of components rather than a few large lots and storing them in bulk over an extended period (Ref. E48). Crude botanical and other ingredients are inherently unstable and may lose their quality in even a short time unless costly temperature, humidity, and light controls are in place (Ref. E49). We also know, however, that some dietary ingredient suppliers produce large amounts and then ship out smaller packages. For dietary supplements produced using part of a large production run of a dietary ingredient, the number of batches per lot could be large. Also, some producers buy a single shipment lot of a raw material and use it in many batches. We assume that as many as 12 batches per shipment lot of dietary ingredient is a plausible maximum. In the cost calculation, we assumed that 1 was minimum and 12 the maximum number of batches produced per lot, with 6.5 the average.

- Number of batches produced

We have survey results (Ref. E2) on the number of batches produced per establishment. According to the survey, very small establishments produce an average of 223 batches per year, small establishments produce an average of 554 batches per year, and large establishments produce an average of 309 batches per year.

- Inprocess potential defects

Inprocess defects involve many of the same potential defects that can occur in components. The more restrictive CGMP option requires inprocess tests at all points where contamination or other defects can occur. Filth, chemicals, microbial pathogens, physical objects, and insects can be introduced into the product during manufacturing. In addition, purity, quality, strength, and composition can be compromised.

- Number of potential inprocess defects

Some processes may have no control points, steps, or stages that involve the potential for defects. If certain manufacturing processes in the production of a dietary supplement can be carried out without being subject to potential defects, no inprocess tests would be required for those processes. We therefore assumed that zero inprocess tests would be the lower bound requirement. For the upper bound, we assumed that no products would have more than five potential control points or steps that could lead to defects. We believe that most production processes will have fewer than 5 control points, so we

assumed an average of 2.5 control points requiring in-process tests for defects.

- Number of required inprocess tests per control point

  We assumed one test per defect per control point.

- Number of ingredients identified per quality test

We had no direct evidence on the number of identity tests per final dietary supplement. For the maximum, we assumed that the number of tests would equal the number of ingredients. The number of ingredients identified per test varies from less than one to a very large number. We assumed that for vitamins and minerals, the minimum number of identity tests would be one and the maximum would be 30, with 2 the most likely. Botanical and herbals are less easily characterized than vitamins; so identifying large numbers of ingredients with a single test would be highly unlikely. We assumed that one to two ingredients would be identified per test for herbal products.

- Number of final product tests per batch

We had no direct evidence on the number of quality tests per final dietary supplement. After adjusting for the possibility of multiple results from a single test, multiple ingredients in single products, and the differing number of ingredients in herbal and vitamin products, we estimated that the proposed rule would require about three tests for identity, purity, quality, strength, and composition for each batch of final product. These

are the only required tests in the proposed rule, but establishments may choose to perform inprocess tests and tests on ingredients in order to prevent waiting until final product testing to discover defects.

iv. Costs per test. We estimated the costs per test partly with published prices of independent laboratories as posted on the Internet (Refs. E50 and E51), and partly from our conversations with FDA and industry experts on testing. We found that testing costs vary according to frequency and complexity. The more frequently technicians perform tests, the lower are the costs per test. Many tests require sophisticated equipment, such as gas chromatography, high pressure liquid chromatography, distillation, extraction, various spectrophotometers, and other types of equipment. Using sophisticated equipment requires trained personnel. Even simple physical or organoleptic testing requires training or experienced personnel. The type of ingredient, compound, or product can also affect the cost because some are easily identified using routine or single step techniques and others require multiple steps or complex techniques, especially if there are similar products that can be mistaken for the products being identified. The type of defect tested for affects the cost; some defects can be found visually if they are found on the surface, but others are latent. Some tests require multiple samples or multiple steps. In addition,

tests require the taking and preparing preparation of samples, whose cost can vary.

We assumed that $20 per test represented a plausible lower bound. This cost represents the full cost of carrying out a test, including collecting and storing the sample, the time for training the personnel who carry out the test, and any associated records. Although some Internet testing prices for tests were as high as $300, we assumed that with frequent testing $150 would be a more plausible upper bound average cost. The majority of listed prices fell into the $20 to $80 range, so we selected $50 (the midpoint) as most likely. The average cost per test was about $60.[8]

Changing our assumption about the midpoint of testing costs would change our estimate of the cost of the rule. If the cost of testing each batch is actually significantly higher, then the

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[8] The average cost is higher than the most likely cost because we modeled costs with a Beta-Pert distribution that was skewed rightward (toward higher costs). The Beta distribution is part of the Bernoulli family of distributions and is closely related to the Binomial. The Binomial gives the distribution of the number of successes (s) in n trials if the probability of the success in each trial is p. The Beta shows the distribution of the value of p when s successes occur in n trials. The Beta-Pert distribution is a Beta distribution that has been rescaled to run between values other than 0 and 1. The Beta-Pert uses a minimum, maximum, and most likely value to generate a distribution running from the minimum to the maximum, with a mean equal to (minimum + (4 x most likely) + maximum)/6. We used the Beta-Pert distribution because we did not have a representative sample to derive the distribution, but we did have enough information to identify a plausible maximum, minimum, and most likely value. The use of the Beta-Pert, then, indicates that we do not know the shape of the probability distribution of possible testing costs, but we do have limited data.

impact to those firms that incur the cost and to society will have been understated.

v. The number and cost of tests: summary. We estimated the number of tests required of the representative manufacturer as a weighted average of the number of tests required for vitamins and minerals and the number of tests required for all other supplements (which were mainly herbal products). We used survey responses to a question about the establishment's primary line of business for the weights used to compute the average number of tests. We dealt with multiple responses by treating all nonvitamin and nonmineral responses as other dietary supplements. The following weights, as shown below, differed by size of manufacturer:

- 24 percent of very small manufacturers produce vitamins and minerals; 76 percent produce other dietary supplements.
- 42 percent of small manufacturers produce vitamins and minerals; 58 percent produce other dietary supplements.
- 69 percent of large manufacturers produce vitamins and minerals; 31 percent produce other dietary supplements.

The annual cost of testing differed by the size of the firm, because the average number of batches produced differed. For the option calling for more strict regulation, the total costs of testing would be much higher than in the proposed rule. The

unadjusted total cost of testing under the more restrictive CGMP option would be:

$148,000 for very small establishments;

$415,000 for small establishments;

$263,000 for large establishments.

We found some corroboration for these estimates in a comment on the Advance Notice of Proposed Rulemaking entitled "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" published in the FEDERAL REGISTER of February 6, 1997 (62 FR 5699 to 5709). According to the comment, the cost of testing components and final products inhouse would be at least $650 per batch plus microbiological tests. Testing costs could be more if establishments sent samples to independent laboratories for testing or if they conducted extensive identity tests of herbal and botanical products. If we apply the $650 to the annual number of batches per establishment, the comment implies that very small establishments would perform $145,000 (223 x $650) worth of tests, small establishments would perform $360,000 (554 x $650) worth of tests, and large establishments would perform $200,000 (309 x $650) worth of tests. These estimates are reasonably close to our simulation estimate.

The unadjusted testing costs represent the total requirements and recommendations, not the additional costs that would be incurred in response to the proposed rule. Tests on

incoming components and inprocess tests would not be required by the proposed rule. Most establishments already conduct some tests, or send samples out for testing. We, therefore, adjusted the estimated testing costs of the proposed rule to include only required tests and to account for the testing costs currently borne voluntarily by manufacturers. The survey results showed how many respondents were conducting various types of tests.

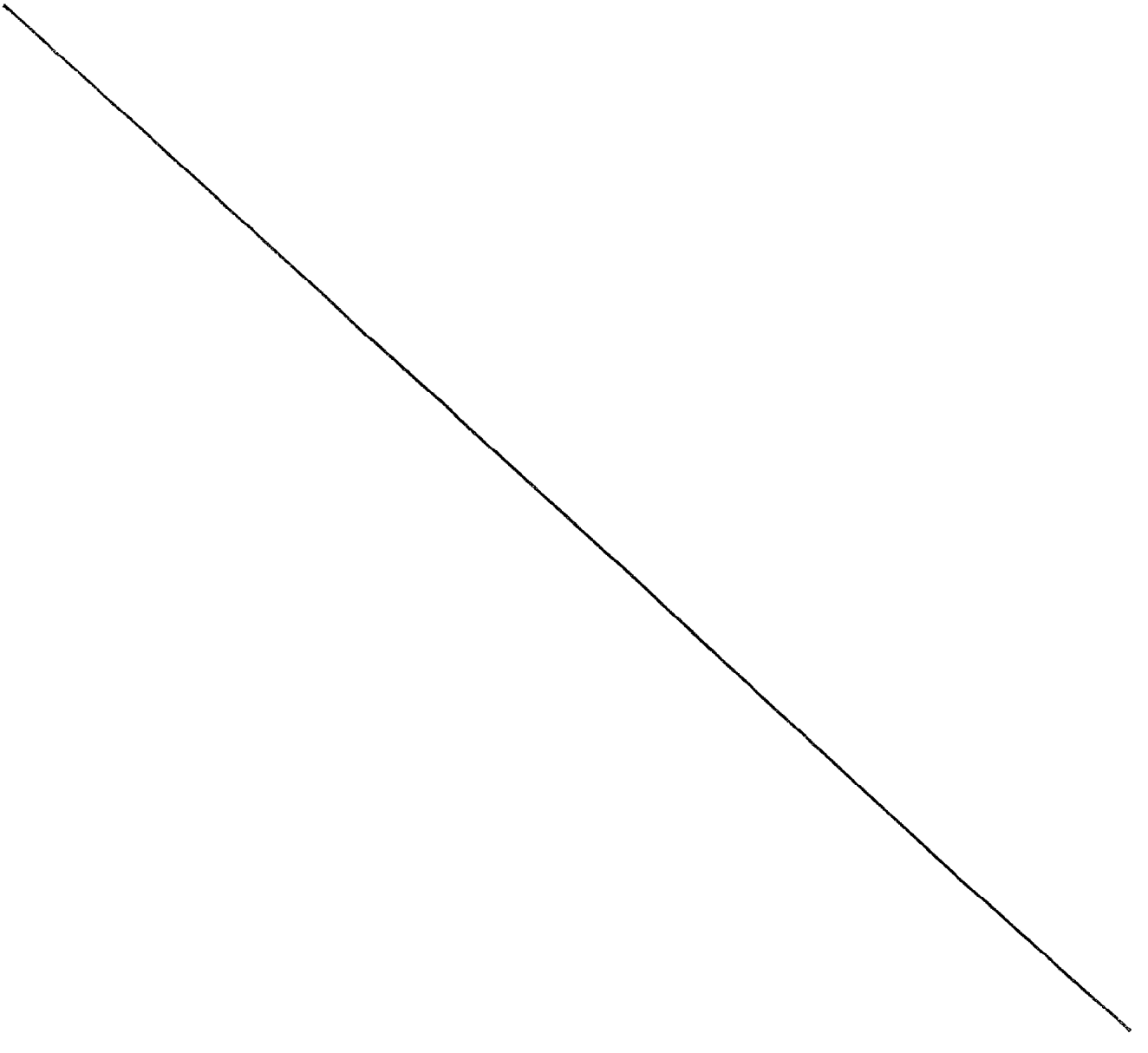

Table 14.--Values Used in Testing Cost Calculations

Name	Value or Distribution Used	Source
Number of dietary ingredients per product batch	Vitamins and minerals--13 All other categories--4	Sample from 3,000 dietary supplement labels (Ref. E46)
Number of identity tests per ingredient lot	1 Identity test per ingredient lot	Assumption based on discussions with industry--FDA requests comments
Number of tests for defects per ingredient lot	0 to 5 tests for defects	Assumption based on discussions with industry--FDA requests comments
Number of unlisted components	0 to 6 components; 4 most likely	Ref. E47
Number of tests per unlisted components	1 identity test per component	Assumption based on discussions with industry--FDA requests comments
Number of shipments (Lots) of ingredients and unlisted components	1 to 12 batches per shipment lot of dietary ingredients	Assumption based on discussions with industry--FDA requests comments (Ref. E48)
Number of batches produced	Very small establishments--223 Small establishments--554 Large--309	Ref. E2
Number of inprocess potential defects	0 to 5 potential control points; 2.5 average	Assumption based on discussions with industry--FDA requests comments
Number of inprocess tests per control point	1 test per defect per control point	Assumption based on discussions with industry--FDA requests comments
Number of ingredients identified per identity test	Vitamins and minerals--1 to 30; 2 most likely All other categories--1 to 2	Assumption based on discussions with industry--FDA requests comments
Number of final product tests per batch	3 tests per batch	Assumption based on discussions with industry--FDA requests comments
Costs per test	Beta pert distribution skewed rightward between $20 to $150; $50 most likely; $60 average	Refs. E50 and E51

vi. Labor costs. We used the average manufacturing wage of $15.65 per hour to estimate the cost of labor. We assumed that various tasks required by the proposed rule would take some number of hours per year, per batch of product, or per square foot of physical plant. For example, we assumed that time spent on the sanitation of physical plants is a function of the square footage. We assumed 1 hour per week for very small establishments, 3 hours per week for small establishments, and 20 hours per week for large establishments.

vii. Other costs. The main costs in this category are for pest and rodent control. We consulted a commercial supplier of these services for the estimated monthly costs, which were $400 to $600 a month for very small establishments, $480 to $720 for small establishments, and $700 to $1,000 for large establishments (Ref. E52). For each size of establishment, we selected the midpoint of the range as the most likely value.

d. Estimating costs. We initially gathered information and made assumptions about the full cost of a provision. We then adjusted these estimates to account for the many activities already being carried out, as well other activities that would not have to be carried out by all establishments. We used the survey to estimate the likelihood that an establishment would incur a cost. To get an estimate of the average cost of provision (adjusted for baseline activities) for each category, we multiplied the average cost per establishment by the probability that the establishment would need to undertake the expense (one minus the probability that the establishment was already doing it). For each provision of the proposed rule, the simulation carried out the following calculation:

Cost per unit of analysis for each provision =

number of units of analysis per establishment x

probability that establishment incurs cost x

adjustment for requirement (yes or no) =

cost per provision per establishment

We estimated both a setup cost (a one-time fixed cost) of the provision and an annual recurring cost. The first-year costs would be the setup costs plus the annual costs. To get the total costs of the rule, we multiplied the number of establishments in each size category (from the survey) by the average costs per establishment in that category. We then adjusted for the establishments that did not respond to the survey but are believed to be in the industry. Two hundred thirty eight establishments responded to the survey; we estimated that 1,566 firms are in the industry. We estimated costs with the following calculation:

[Number of very small establishments x costs per very small establishment) +

(number of small establishments x costs per small establishment) +

(number of large establishments x costs per large establishment)] x

adjustment for establishments not in survey

The rule is complex and the industry is made up of very different kinds of firms, so cost estimates are averages with, in some cases, large variances. The cost per unit, number of batches and employees, and probability that the establishment would incur the cost all contain uncertainty. The values in table 15 of this

document are used in the cost estimates, and are generated from multiple sources.

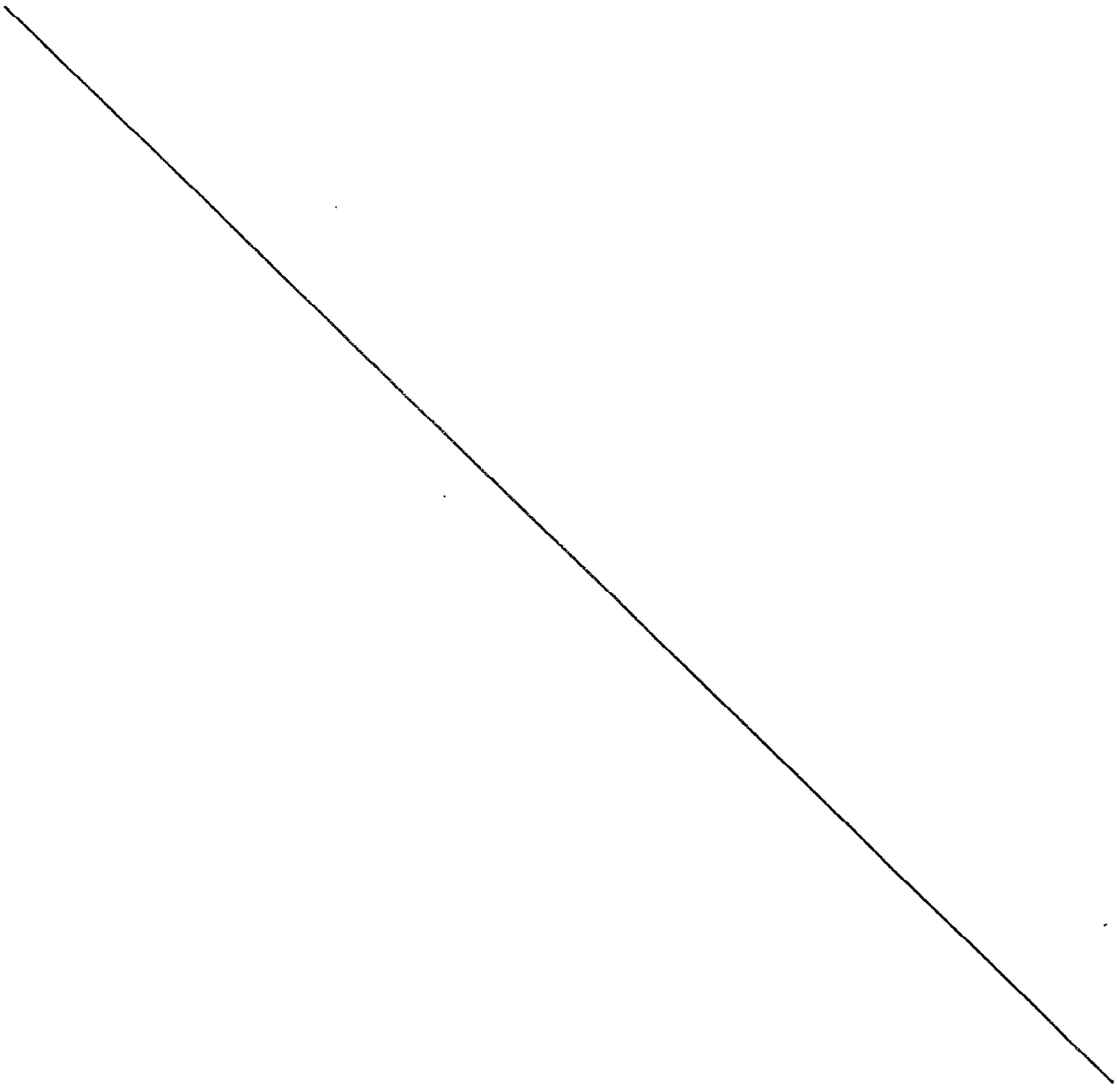

Table 15.--Values Used in Cost Calculations

Name	Value or Distribution Used	Source
Average wage per hour	$15.65	Employment Index, Bureau of Labor Statistics

Average size of establishments in square feet	very small = 24,674;
	small = 71,354;
	large = 596,000
		Ref. E2

Average number of employees	very small = 7.6;
	small = 95;
	large = 1,005
		Ref. E2

Average annual number of batches	very small = 223;
	small = 554;
	large = 309
		Ref. E44

Annual time recordkeeping	1/10 of setup time per provision	Ref. E44
Personnel sanitation	1 hour per week per worker	Assumption, based on requirements of proposed rule
Sanitation time for physical plant	1 hour per week for very small establishments; 3 hours per week for small establishments; 20 hours for physical plant per week for large establishments	Assumption, based on difference in average physical plant size
Sanitation supervisor	Very small and small establishments = 1 hour per week; large establishments = 1 hour per week	Assumption, based on number of workers
Pest control setup costs	$1,500 to $2,000 for very small establishments; $1,800 to $2,400 for small establishments; $2,600 to $3,400 for large establishments. Average for each size establishment was midpoint ($1,750, $2,100, $3,000)	Ref. E52
Pest control annual costs	$400 to $600 per month for very small establishments; $480 to $720 for small establishments; $700 to $1,000 for large establishments. Average for each size establishment was the midpoint ($500, $600, $850)	Ref. E52
Renovation cost	$50 per square foot; with 0 to 20 percent of physical plant to be renovated, with 10 percent most likely	Based on construction costs and square feet
Minimum quality control unit	1 person or 1 percent of establishment work force	Assumption based on requirements of proposed rule
Equipment replacement	For very small establishments, 0 to $1,000, with $100 most likely; small, 0 to $10,000, with $1,000 most likely; large, 0 to $100,000 with $1,000 most likely	Assumption, based on size of establishments
Setup costs for automatic equipment	$500 for hardware, 16 hours	Software costs and assumptions about labor hours

Table 15.--Values Used in Cost Calculations (Continued)

Name	Value or Distribution Used	Source
Annual costs for automatic equipment	1 to 2 hours per month for very small and small establishments; 2 to 4 hours per month for large establishments	Assumption based on average size of establishments
Sanitation of equipment and surfaces	5 hours per week for very small establishments, 15 hours per week for small establishments, 100 hours per week for large establishments	Assumption based on average sizes of establishments
Number of dietary ingredients per batch, supplements other than vitamins	12.8; standard deviation = 15.6	Ref. E46
Number of dietary ingredients per batch, supplements other than vitamins	3.6; standard deviation = 4.8	Ref. E46
Cost per test	$20 to $150, with $50 most likely	See text discussion
Holding products and dietary ingredients: capital requirements	Setup cost for very small 0 to $1,000, with $100 most likely. Multiply by 3 for small establishments and by 20 for large establishments	Based on average sizes of establishments
Default probabilities that establishments are not currently acting in accordance with a provision	For very small establishments, 0.2; for small establishments, 0.1, for large establishments, 0.01	Based on results of survey for other practices

We combined the costs per establishment with the number of establishments and probabilities from the survey, and adjusted for establishments not in the survey to estimate the total costs of the proposed rule. Table 16 of this document summarizes the estimated total costs for very small establishments, small establishments, large establishments, and warehouses. Table 17 of this document shows the total costs for the first year and annually after the first year, assuming that the proposed rule is phased in over 3 years. Table 18 of this document shows the total costs of the proposed rule compared to the total costs of other options.

Table 16.--Summary of Costs by Size of Establishment

	Number of Establishments	1st Year Costs per Establishments	Annual Costs per Establishments	Total 1st Year Costs	Total Annual Costs
Very small establishments	740	$62,000	$38,000	$46 million	$28 million
Small establishments	766	$99,000	$61,000	$76 million	$47 million
Large establishments	60	$83,000	$47,000	$5 million	$3 million
Warehouses and other holders	26,617	$436	$342	$12 million	$9 million

Table 17.--Estimated Total Costs

	1st Year	2nd Year	3rd Year	4th Year and After
Very small establishments	0	0	$46 million	$28 million
Small establishments	0	$76 million	$47 million	$47 million
Large establishments	$5 million	$3 million	$3 million	$3 million
Warehouses	$12 million	$9 million	$9 million	$9 million
Total	$17 million	$88 million	$105 million	$87 million

8. Summary of Benefits and Costs

We estimated that, once it is fully implemented, the measured annual benefits from the proposed rule would be $218 million; measured annual costs would be about $86 million. Additional but unmeasured benefits should also be recognized when comparing the total costs and benefits. Table 18 of this document compares the benefits and costs of the proposed rule to the benefits and costs of the leading regulatory options. Because the phase in period, complicates the comparison for the early years, we limit the comparison to annual benefits once all establishments are covered.

Table 18.--Annual Benfits and Costs of Regulatory Options

Regulatory Option	Annual Benefits	Annual Costs
Proposed rule	$218 million	$86 million
Fewer requirements for vitamins and minerals	$109 million	$69 million
Stricter CGMP	$218 million	$178 million
HACCP only	$42 million	$38 million
Testing only	unable to estimate	$32 million
High risk products only	unable to estimate	less than $86 million

Uncertainties in the analysis. In this section, we list many of the assumptions that we made and, if varied, could change the estimates of costs and benefits significantly. Such changes could have significance for the construction of any potential final rule. Therefore, we ask that comments address these aspects of the analysis and, where possible, provide FDA with better data to reduce the uncertainty. We estimated the benefits using indirect measures of the frequency of illness associated with poor manufacturing practices. These indirect measures required several assumptions that, when combined, produced our estimates. With the exception of the recall benefit, which is based directly on FDA recall records, each component of estimated benefits involves assumptions that reflect our uncertainty. For the health benefits, the assumption that the number or illnesses was 100 times the number of recalls is important, because varying the multiplier greatly varies the health benefits. For the rare catastrophic event model, the assumption that an event would occur every 30 years mattered to the estimated benefits. Indeed, if the event was a one-time occurrence, the benefits from the prevention of the catastrophic health event would be zero. Our hypothetical search model used assumptions at each step, and those benefits change when the assumptions change, as we show below.

The costs of the rule depend on our assumptions about the amount and cost of testing. The amount of testing is highly uncertain; we have tried to model the number of tests based on number of ingredients and types of tests.

We first characterized the uncertainty as a probability distribution. We ran 1,000 computer simulations to estimate both benefits and costs. The simulations used distributions and assumptions from tables 8 through 13 of this document in place of single estimates.

Table 19.--Distribution of Simulation Results for Annual Benefits and Costs

	5th Percentile	Median	Mean	95th Percentile
Annual benefits	$89 million	$198 million	$218 million	$405 million
Annual costs	$62 million	$80 million	$86 million	$128 million

The computer simulation gives the distribution of estimated benefits and costs. If the underlying distributions capture the uncertainty of the estimates, then the results in table 19 of this document give a clear picture of the uncertainty. Another way to show the uncertainty is to see how sensitive the results are to plausible changes in individual variables. We start with benefits.

Table 20.--Sensitivity of Benefits

Description	Estimated Annual Benefits
The proposed rule	$218 million
If reporting rate of illness is 0.1 (baseline is 0.01)	$182 million
If reporting rate of illness is 0.005 (baseline is 0.01)	$257 million
If the value of a statistical life is $3 million (baseline is $5 million)	$175 million
If the value of a statistical life is $7 million (baseline is $5 million)	$259 million
If consumer search time per item is 1 minute (baseline is 3.75 minutes)	$137 million
If consumer search time per item is 5 minutes (baseline is 3.75 minutes)	$250 million
If consumer search time equals 40 percent of shopping time (baseline is 70 percent)	$166 million
If consumer search time is equal to shopping time (baseline is 70 percent)	$254 million
If consumer search for quality accounts for 30 percent of search time (baseline is 20 percent)	$278 million
If consumer search time for quality accounts for 10 percent of search time (baseline is 20 percent)	$158 million
If catastrophic events are not prevented (baseline is $66 million annual benefit from prevention)	$152 million

We mainly looked at the cost effects of changing assumptions about testing and consumer complaints. As table 21 of this document shows, annual costs are quite sensitive to the assumptions about the average cost and number of tests.

Table 21.--Sensitivity of Costs

Description	Estimated Annual Costs
The proposed rule	$86 million
6 tests per batch (baseline is 3)	$119 million
1 test per batch (baseline is 3)	$66 million
$100 per test (baseline is $60)	$101 million
1 consumer complaint per 20 batches (baseline is 1 per 10)	$77 million
1 consumer complaint per 5 batches (baseline is 1 per 10)	$104 million

C. Initial Regulatory Flexibility Analysis

1. Introduction

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601-612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would

lessen the economic effect of the rule on small entities. We find that this proposed rule would have a significant economic impact on a substantial number of small entities.

2. Economic Effects on Small Entities

a. Number of small entities affected. The proposed regulations would affect many small entities. Our classification of establishment size is based on the Small Business Administration's definition for small, as discussed previously in this document. A small business by this definition is any establishment with fewer than 500 employees. For this analysis, we defined very small establishments as establishments with fewer than 20 employees. Some small and very small establishments produce very large revenues and would probably not incur a large decline in profitability from the proposed CGMP regulations. We lack precise information about those establishments. Based on the survey, we estimated that 830 establishments, 53 percent of the total establishments, could be classified as very small (under 20 employees) and 564 as small (20 to 499 employees), which is 36 percent of the total establishments.

We estimated that 95 percent of all holders (warehouses and wholesalers) covered by this regulation are small using the Small Business Administration definition. The total number of holders likely to be affected by this regulation is 26,617 (see table 4

of this document), so the total number of holders that are small would be 25,286 (= 0.95 x 26,617).

The small establishments that would be affected by the proposed regulations are those establishments that would have to perform the various required activities, and that would not have done so without the regulations. As in the preliminary regulatory impact analysis (section VII.B of this document), we determined our estimate of baseline (pre-CGMP) manufacturing practices with the survey of the industry (Ref. E2). The survey asked representative respondents to answer a series of questions, including how many employees they had and what their existing practices were. From the survey, we determined that small establishments do not now follow all of the provisions of the proposed CGMP regulations now. Those that do not follow the proposed requirements will incur a cost to do so.

b. Costs to small entities. Implementation costs vary across establishments based on current practices and the types of products manufactured, packaged, or held. We estimated the range of current practices using the survey of the industry. The cost model divided establishments by size, which allowed us to estimate the distribution of costs per establishment for each size and product class. Table 22 of this document shows the cost per establishment for very small and small establishments. For comparison, we include the estimated average cost per large

establishment and the median revenues for each size category. As the table shows, costs per establishment are proportionally higher for very small than for large establishments. The table's most striking result is that costs are highest for small (20 to 499 employees) establishments.

Table 22.--Cost Per Establishment

	1st year	Annual
Very small--fewer than 20 employees; median revenue under $1 million	$62,000	$38,000
Small--20 to 499 employees; median revenue $5 to 10 million	$99,000	$61,000
Large--500 or more employees; median revenue $20 to $50 million	$83,000	$47,000

Small establishments that do not perform a substantial number of the actions required by the proposed CGMP regulations would bear relatively high costs for compliance with the provisions of this proposed rule. As shown in table 22 of this document, we estimated the average annual compliance costs for a very small establishment to be around $38,000. About one-third of those establishments or about 500 firms have annual sales revenues under $500,000. In addition, the average annual compliance cost for a small establishment is around $61,000. As the survey indicated, about 14 percent of establishments with 20 to 499 employees or about 200 firms have annual sales revenues under $500,000. For purposes of our analysis, we regard firms with revenues of $500,000 or less to be low revenue firms. Although the proposed rule would raise product prices, the price increase (which would largely be determined by changes made by large establishments) would be much smaller than the increase in

the average costs of very small producers. The average burden to very small low revenue firms, then, would be at least 8 percent of their annual revenue. The average burden to small low revenue firms would be at least 12 percent of annual revenue. Establishments with above average costs, and even establishments with average costs, would be hard pressed to continue to operate. Therefore, some of these establishments, for example, such as those that produce other products (foods or pharmaceuticals) or are part of firms with more than one establishment, may decide it is too costly and either change product lines or go out of business. If we assume that one half of these firms have sales revenues from other products and locations and remove them from the at-risk group, we are left with approximately 350 very small and small establishments with less than $500,000 in revenue. It is possible that a large number of these 350 very small and small establishments would be unable to absorb the compliance costs and will close.

3. Regulatory Options

a. Exemptions for small entities. The burden on small establishments would be reduced if they were exempt from some provisions of the proposed rule. Most entities affected by this proposed rule, however, are small. Exempting small establishments from some or all of its provisions would be likely to reduce benefits.

b. Longer compliance periods. Lengthening the compliance period would provide regulatory relief for small entities. A longer compliance period for small entities would allow additional time for setting up recordkeeping, making capital improvements to the physical plant, purchasing new or replacement equipment, and other one-time expenditures. It would also delay the impact of the annual costs of compliance. We have given very small and small firms an additional 2 years for compliance. The proposed rule, then, would be phased-in over 3 years, with large firms complying after 1 year, and both very small and small firms after 3 years. After 3 years, the annual costs would be incurred. The cost savings of delay may well be larger than simply the present value of the delay because very small and small firms may also be able to reduce their compliance costs by taking advantage of increases in industry knowledge and experience in implementing CGMP regulations. A summary of the compliance costs is shown in table 22 of this document.

Although lengthening the compliance period would provide some regulatory relief to small entities, relief for these provisions would also delay the full realization of the benefits of the proposed rule.

4. Description of Recordkeeping and Reporting

The Regulatory Flexibility Act requires a description of the recordkeeping and recording required for compliance with this

proposed rule. This proposed rule would require the preparation of records. As described in the Preliminary Regulatory Impact Analysis, records must be written or electronic documents must be kept that demonstrate that specific action or actions occurred in the manufacturing process in compliance with the proposed regulations. Records that would be required in this proposed rule would demonstrate, that corrective actions were taken, that equipment, instruments, and controls used in laboratory operations and quality control were installed properly, and calibrated; that maintenance programs were followed; and that the results of any testing meet the necessary specifications.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use the new documents is a recurring cost depending on how frequently documents are modified, how often personnel turn over, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate multiplied by the expected labor hours necessary to perform a written or electronic record and the time necessary for management to review the records to see that actions are documented accurately. In addition, electronic records necessitate recurring time spent ensuring that the equipment is serviced and maintained properly.

5. Summary

The proposed CGMP regulations would have a significant economic impact on a substantial number of small entities.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We consulted with seven State officials to make a tentative determination about whether this proposed rule would have federalism implications. Based on this consultation, it does not appear that this proposed rule has federalism implications. In addition, we sent a letter on March 7, 2000, to elected State officials and their representative organization to notify them that our unified agenda was published on November 22, 1999, and identified this proposed CGMP rule as a rule that would publish in the year 2000. In that letter, we solicited comments on any federalism implications that this proposed rule may have. To date, no responses have been received to our solicitation. After publishing this proposed rule, FDA will send a letter to elected State officials and their representative organization requesting consultation about any federalism implications. We invite comment on our tentative determination that this proposed rule does not have federalism implications, and therefore, does not contain policies that have substantial direct effects on the

States, or on the distribution of power and responsibilities among the various levels of government.

IX. Request for Comments

Interested persons may submit to the Dockets Management Branch (see ADDRESSES) written comments regarding this proposal by [insert date 90 days after date of publication in the FEDERAL REGISTER]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

X. References

We have placed the following references on display in the Dockets Management Branch (see ADDRESSES). You may see them between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects

21 CFR Part 111

Dietary foods, Drugs, Foods, Packaging and containers.

21 CFR Part 112

Drugs, Packaging and containers, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR chapter I, parts 111 and 112 as set forth below:

PART 111--CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS

1. The authority citation for part 111 is revised to read as follows:

AUTHORITY: 21 U.S.C. 321, 342, 343, 348, 371, 374, 381, 393; 42 U.S.C. 264.

2. The part heading for part 111 is revised as set forth above.

3. Add new subpart A to part 111 to read as follows:

Subpart A--General Provisions

Sec.

111.1 Who is subject to these regulations?

111.2 What are these regulations intended to accomplish?

111.3 What definitions apply to this part?

111.5 Do other statutory provisions and regulations apply?

111.6 Exclusions.

Subpart A--General Provisions

§ 111.1 Who is subject to these regulations?

You are subject to these regulations if you manufacture, package, or hold a dietary ingredient or dietary supplement.

§ 111.2 What are these regulations intended to accomplish?

These regulations establish the minimum current good manufacturing practices that you must use to the extent that you manufacture, package, or hold a dietary ingredient or dietary supplement.

§ 111.3 What definitions apply to this part?

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in these regulations. For the purpose of these regulations, the following definitions also apply:

Actual yield means the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement.

Batch means a specific quantity of a dietary ingredient or dietary supplement that is intended to meet specifications for identity, purity, quality, strength, and composition, and is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.

Batch number, lot number, or control number means any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, or holding of a batch or lot of dietary ingredients or dietary supplements can be determined.

Component means any substance intended for use in the manufacture of a dietary ingredient or dietary supplement including those that may not appear in the finished dietary ingredient or dietary supplement. Component includes ingredients and dietary ingredients as described in section 201(ff) of the act.

Consumer complaint means communication that contains any allegation, written or oral, expressing dissatisfaction with the quality of a dietary ingredient or a dietary supplement related to good manufacturing practices. Examples of product quality related to good manufacturing practices are: Foul odor, off taste, superpotent, subpotent, wrong ingredient, drug contaminant, other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead), disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, or mislabeling. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint

does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.

Contact surface means any surface that contacts a component, dietary ingredient, dietary supplement, and those surfaces from which drainage onto the component, dietary ingredient, dietary supplement, or onto surfaces that contact the component, dietary ingredient, or dietary supplement ordinarily occurs during the normal course of operations. Examples of contact surfaces include, but are not limited to, containers, utensils, tables, contact surfaces of equipment, and packaging.

Ingredient means any substance that is used in the manufacture of a dietary ingredient or dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as described in section 201(ff) of the act.

Inprocess material means any material that is fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary ingredient or dietary supplement.

Lot means a batch, or a specific identified portion of a

batch intended to have uniform identity, purity, quality, strength, and composition; or, in the case of a dietary ingredient or dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is intended to have uniform identity, purity, quality, strength, and composition.

Microorganisms means yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern. This definition includes, but is not limited to, species that:

(1) Have public health significance;

(2) Could cause a component, dietary ingredient, or dietary supplement to decompose;

(3) Indicate that the component, dietary ingredient, or dietary supplement is contaminated with filth; or

(4) Otherwise may cause the component, dietary ingredient, or dietary supplement to be adulterated.

Must is used to state mandatory requirements.

Pest means any objectionable insects or other animals including, but not limited to, birds, rodents, flies, mites, and larvae.

Physical plant means all or parts of a building or facility used for or in connection with manufacturing, packaging, or holding a dietary ingredient or dietary supplement.

Quality control means a planned and systematic operation or procedure for preventing a dietary ingredient or dietary supplement from being adulterated.

Quality control unit means any person or group that you designate to be responsible for quality control operations.

Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to ensure that the sample accurately portrays the material being sampled.

Reprocessing means using, in the manufacture of a dietary ingredient or a dietary supplement, clean, unadulterated components, dietary ingredients, or dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions and that have been made suitable for use in the manufacture of a dietary ingredient or dietary supplement.

Sanitize means to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

Theoretical yield means the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.

You means a person who manufactures, packages, or holds dietary ingredients or dietary supplements.

Water activity (a_w) is a measure of the free moisture in a component, dietary ingredient, or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

We means the United States Food and Drug Administration (FDA).

§ 111.5 Do other statutory provisions and regulations apply?

In addition to these regulations, you must comply with other applicable statutory provisions and regulations under the act related to the manufacturing, packaging, or holding of dietary ingredients or dietary supplements.

§ 111.6 Exclusions.

These regulations do not apply to a person engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary ingredient or dietary supplement by other persons.

4. Add new subpart B to part 111 to read as follows:

Subpart B--Personnel

111.10 What microbial contamination and hygiene requirements apply?

111.12 What personnel qualification requirements apply?

111.13 What supervisor requirements apply?

Subpart B--Personnel

§ 111.10 What microbial contamination and hygiene requirements apply?

(a) Microbial contamination. You must take measures to exclude from any operations any person who might be a source of microbial contamination of any material including components, dietary ingredients, dietary supplements, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. Such measures include, but are not limited to, the following:

(1) Excluding any person who, by medical examination or supervisory observation, is shown to have, or appears to have an illness, open lesion, or any other abnormal source of microbial contamination, which may be expected to result in microbial contamination of components, dietary ingredients, dietary supplements, or contact surfaces, from working in any operations until the condition is corrected; and

(2) Instructing your employees to notify their supervisor(s) if they have or if there is a reasonable possibility that they

have a health condition described in paragraph (a)(1) of this section that could contaminate any components, dietary ingredients, dietary supplements, or any contact surface.

(b) Hygienic practices. If you work in operations during which adulteration of the component, dietary ingredients, dietary supplement, or contact surface may occur, you must use hygienic practices to the extent necessary to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces. These hygienic practices include, but are not limited to:

(1) Wearing outer garments in a manner that protects against the contamination of components, dietary ingredients, dietary supplements, or any contact surface;

(2) Maintaining adequate personal cleanliness;

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:

(i) Before starting work;

(ii) After each absence from the work station; and

(iii) At any other time when the hands may have become soiled or contaminated;

(4) Removing all unsecured jewelry and other objects that might fall into components, dietary ingredients, dietary supplements, equipment, or packaging, and removing hand jewelry

that cannot be adequately sanitized during periods in which components, dietary ingredients, or dietary supplements are manipulated by hand. If hand jewelry cannot be removed, it must be covered by material that is maintained in an intact, clean, and sanitary condition and that effectively protects against contamination of components, dietary ingredients, dietary supplements, or contact surfaces;

(5) Maintaining gloves used in handling components, dietary ingredients, or dietary supplements in an intact, clean, and sanitary condition. The gloves must be of an impermeable material;

(6) Wearing, where appropriate, in an effective manner, hair nets, caps, beard covers, or other effective hair restraints;

(7) Not storing clothing or other personal belongings in areas where components, dietary ingredients, or dietary supplements or any contact surfaces are exposed or where contact surfaces are washed;

(8) Not eating food, chewing gum, drinking beverages and using tobacco products in areas where components, dietary ingredients, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed; and

(9) Taking any other precautions necessary to protect against the contamination of components, dietary ingredients, dietary supplements, or contact surfaces with microorganisms,

filth, or any other extraneous materials, including, but not limited to, perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.

§ 111.12 What personnel qualification requirements apply?

(a) You must have qualified employees to manufacture, package, or hold dietary ingredients or dietary supplements; and

(b) Each person engaged in manufacturing, packaging, or holding must have the training and experience to perform the person's duties.

§ 111.13 What supervisor requirements apply?

(a) You must assign qualified personnel to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements.

(b) You and the supervisors you use must be qualified by training and experience to supervise.

5. Add new subpart C to part 111 to read as follows:

Subpart C--Physical Plant

111.15 What sanitation requirements apply to your physical plant?

111.20 What design and construction requirements apply to your physical plant?

Subpart C--Physical Plant

§ 111.15 What sanitation requirements apply to your physical plant?

(a) Physical plant facilities. (1) You must maintain your physical plant in a clean and sanitary condition; and

(2) You must keep your physical plant in repair sufficient to prevent components, dietary ingredients, dietary supplements, or contact surfaces from becoming contaminated.

(b) Cleaning compounds, sanitizing agents, and pesticides. (1) You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use.

(2) You must not use or hold toxic materials in a physical plant in which contact surfaces, components, dietary ingredients, or dietary supplements are manufactured or exposed, unless those materials are necessary:

(i) To maintain clean and sanitary conditions;

(ii) For use in laboratory testing procedures;

(iii) For maintaining or operating the physical plant or equipment; or

(iv) For use in the plant's operations.

(3) You must identify and hold toxic cleaning compounds, sanitizing agents, pesticides, and pesticide chemicals in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or contact surfaces.

(c) Pest control. (1) You must not allow animals or pests in any area of your physical plant. Guard or guide dogs are

allowed in some areas of your physical plant if the presence of the dogs will not result in contamination of components, dietary ingredients, dietary supplements, or contact surfaces;

(2) You must take effective measures to exclude pests from the physical plant and to protect against contamination of components, dietary ingredients, dietary supplements, and contact surfaces on the premises by pests; and

(3) You must not use insecticides, fumigants, fungicides, or rodenticides, unless you take precautions to protect against the contamination of components, dietary ingredients, dietary supplements, or contact surfaces.

(d) Water supply. (1) You must provide water that is safe and of adequate sanitary quality, at suitable temperatures, and under pressure as needed, in all areas where water is necessary for:

(i) Manufacturing dietary ingredients or dietary supplements;

(ii) Making ice that comes in contact with components, dietary ingredients, dietary supplements, or contact surfaces;

(iii) Cleaning any surface; and

(iv) Employee bathrooms and hand-washing facilities.

(2) Water that contacts components, dietary ingredients, dietary supplements, or any contact surface must at a minimum comply with the National Primary Drinking Water regulations

prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements;

(3) You must have documentation or otherwise be able to show that water that contacts components, dietary ingredients, dietary supplements, or any contact surface meets the requirements in paragraph (d)(2) of this section.

(e) Plumbing. The plumbing in your physical plant must be of an adequate size and design and be adequately installed and maintained to:

(1) Carry sufficient amounts of water to required locations throughout the physical plant;

(2) Properly convey sewage and liquid disposable waste from your physical plant;

(3) Avoid being a source of contamination to components, dietary ingredients, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition;

(4) Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor; and

(5) Not allow backflow from, or cross connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary ingredients or dietary supplements, for cleaning contact

surfaces, or for use in bathrooms or hand-washing facilities.

(f) Sewage disposal. You must dispose of sewage into an adequate sewage system or through other adequate means.

(g) Bathrooms. You must provide your employees with adequate, readily accessible bathrooms. The bathrooms must be kept clean and must not become a potential source of contamination to components, dietary ingredients, dietary supplements, or contact surfaces. You must:

(1) Keep the bathrooms in good repair at all times;

(2) Provide self-closing doors; and

(3) Provide doors that do not open into areas where components, dietary ingredients, dietary supplements, or contact surfaces are exposed to airborne contamination except where alternate means have been taken to protect against contamination (such as double doors or positive airflow systems).

(h) Hand-washing facilities. You must provide hand-washing facilities that are adequate, convenient, and furnish running water at a suitable temperature. You must do this by providing:

(1) Hand-washing and, where appropriate, hand-sanitizing facilities at each location in your physical plant where good hygienic practices require employees to wash or to sanitize or both wash and sanitize their hands;

(2) Effective hand-cleaning and sanitizing preparations;

(3) Air driers, sanitary towel service, such as disposable

paper towels, or other suitable drying devices;

(4) Devices or fixtures, such as water control valves, designed and constructed to protect against recontamination of clean, sanitized hands;

(5) Signs that are easy to understand and are posted throughout the physical plant that direct employees handling components, dietary ingredients, dietary supplements, or contact surfaces to wash and, where appropriate, to sanitize their hands before they start work, after each absence from their duty station, and when their hands may have become soiled or contaminated; and

(6) Trash bins that are constructed and maintained in a manner to protect against recontamination of hands and contamination of components, dietary ingredients, dietary supplements, or any contact surface.

(i) Trash disposal. You must convey, store, and dispose of trash to:

(1) Minimize the development of odor;

(2) Minimize the potential for the trash to attract, harbor, or become a breeding place for pests;

(3) Protect against contamination of components, dietary ingredients, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and

(4) Control hazardous waste to prevent contamination of

components, dietary ingredients, dietary supplements, and contact surfaces.

(j) Sanitation supervisors. You must assign one or more employees to supervise overall sanitation. These supervisors must be qualified by training and experience to develop and supervise sanitation procedures.

§ 111.20 What design and construction requirements apply to your physical plant?

Any physical plant you use in the manufacture, packaging, or holding of dietary ingredients or dietary supplements must:

(a) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;

(b) Have adequate space for the orderly placement of equipment and holding materials as is necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mixups of components, dietary ingredients, and dietary supplements during manufacturing, packaging, or holding;

(c) Permit the use of proper precautions to reduce the potential for mixups or contamination of components, dietary ingredients, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other extraneous material. Your physical plant must have and you must use separate or defined areas of adequate size or other control systems, such as computerized inventory controls or automated systems of

separation, to prevent contamination and mixups of components, dietary ingredients, and dietary supplements during the following operations:

(1) Receiving, identifying, holding, and withholding from use, components, dietary ingredients, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, or holding of dietary ingredients and dietary supplements;

(2) Separating, as necessary, components, dietary ingredients, dietary supplements, packaging, and labels that are to be used from components, dietary ingredients, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection;

(3) Separating the manufacturing, packaging, and holding of different product types including, but not limited to, different types of dietary ingredients, dietary supplements and other foods, cosmetics, and pharmaceutical products;

(4) Performing laboratory analyses and holding laboratory supplies and samples;

(5) Cleaning and sanitizing contact surfaces;

(6) Packaging and label operations; and

(7) Holding dietary ingredients or dietary supplements.

(d) Be designed and constructed in a manner that prevents

contamination of components, dietary ingredients, dietary supplements, or contact surfaces. The design and construction must include, but not be limited to:

(1) Floors, walls, and ceilings that are of smooth and hard surfaces that can be adequately cleaned and kept clean and in good repair;

(2) Fixtures, ducts, and pipes that do not contaminate components, dietary ingredients, dietary supplements, or contact surfaces by dripping or condensate;

(3) Adequate ventilation or environmental control equipment such as air flow systems, including filters, fans, and other air-blowing equipment, that minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate components, dietary ingredients, dietary supplements, or contact surfaces;

(4) Fans and other air-blowing equipment located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces;

(5) Equipment that controls temperature and humidity; and

(6) Aisles or working spaces between equipment and walls that are adequately unobstructed and of adequate width to permit all persons to perform their duties and to protect against contamination of components, dietary ingredients, dietary

supplements, or contact surfaces with clothing or personal contact.

(e) Provide adequate light in:

(1) All areas where components, dietary ingredients, or dietary supplements are examined, processed, or held;

(2) All areas where contact surfaces are cleaned; and

(3) Hand-washing areas, dressing and locker rooms, and bathrooms.

(f) Use safety-type light bulbs, fixtures, skylights, or other glass that is suspended over exposed components, dietary ingredients, or dietary supplements in any step of preparation, unless otherwise constructed in a manner that will protect against contamination of components, dietary ingredients, or dietary supplements in case of glass breakage.

(g) Provide protection by any effective means against contamination of components, dietary ingredients, and dietary supplements in bulk fermentation vessels, including consideration of:

(1) Use of protective coverings;

(2) Placement in areas where you can eliminate harborages for pests over and around the vessels;

(3) Placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and

(4) Use of skimming equipment.

(h) Use adequate screening or other protection against pests, where necessary.

6. Add new subpart D to part 111 to read as follows:

Subpart D--Equipment and Utensils

111.25 What requirements apply to the equipment and utensils you use?

111.30 What requirements apply to automatic, mechanical, or electronic equipment?

Subpart D--Equipment and Utensils

§ 111.25 What requirements apply to the equipment and utensils you use?

(a)(1) You must use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained. Equipment and utensils include, but are not limited to, the following:

(i) Equipment used to hold or convey;

(ii) Equipment used to measure;

(iii) Equipment using compressed air or gas;

(iv) Equipment used to carry out processes in closed pipes and vessels; and

(v) Equipment used in automatic, mechanical, or electronic systems.

(2) You must use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components, dietary ingredients, or dietary supplements with:

(i) Lubricants;

(ii) Fuel;

(iii) Coolants;

(iv) Metal or glass fragments;

(v) Filth or any other extraneous material;

(vi) Contaminated water; or

(vii) Any other contaminants.

(3) All equipment and utensils you use must be:

(i) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;

(ii) Corrosion-resistant if the equipment or utensils contact components, dietary ingredients, or dietary supplements;

(iii) Made of nontoxic materials;

(iv) Designed and constructed to withstand the environment of their intended use, the action of components, dietary ingredients, or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and

(v) Maintained to protect components, dietary ingredients, and dietary supplements from being contaminated by any source.

(4) Equipment and utensils you use must have seams that are

smoothly bonded or maintained to minimize accumulation of component, dietary ingredient, or dietary supplement particles, dirt, filth, organic material, or any other extraneous materials or contaminants to minimize the opportunity for growth of microorganisms.

(5) Each freezer and cold storage compartment you use to hold components, dietary ingredients, or dietary supplements:

(i) Must be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that shows the temperature accurately within the compartment; and

(ii) Must have an automatic device for regulating temperature or an automatic alarm system to indicate a significant temperature change in a manual operation.

(6) Instruments or controls used in the manufacturing, packaging, or holding of a dietary ingredient or dietary supplement, including but not limited to, instruments or controls you use to measure, regulate, or record temperatures, hydrogen-ion concentration (pH), water activity, or other conditions that control or prevent the growth of microorganisms or other contamination must be:

(i) Accurate and precise;

(ii) Adequately maintained; and

(iii) Adequate in number for their designated uses.

(7) Compressed air or other gases you introduce

mechanically into or onto a component, dietary ingredient, dietary supplement, or contact surface or that you use to clean any contact surface must be treated in such a way that the component, dietary ingredient, dietary supplement, or contact surface is not contaminated.

(b)(1) You must calibrate instruments and controls you use in manufacturing or testing a component, dietary ingredient, or dietary supplement.

(2) You must calibrate before first use; and

(i) As specified in writing by the manufacturer of the instrument and control, or

(ii) At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

(c) The person who performs the instrument or control calibration established in accordance with this section must document at the time of performance that the calibration was performed. The documentation must include, but not be limited to:

(1) The instrument or control calibrated;

(2) The date of calibration;

(3) The reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy;

(4) The calibration method used including appropriate

limits for accuracy and precision of instruments and controls when calibrating;

(5) The calibration reading or readings found; and

(6) The recalibration method used if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and

(7) The initials of the person who performed the calibration.

(d) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

(e)(1) You must maintain, clean, and sanitize as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients, or dietary supplements. Equipment and utensils must be taken apart as necessary for thorough maintenance, cleaning, and sanitizing.

(2) You must ensure that all contact surfaces used for manufacturing or holding of low-moisture components, dietary ingredients, or dietary supplements are in a dry and sanitary condition at the time of use. When the surfaces are wet-cleaned, they must be sanitized, when necessary, and thoroughly dried before subsequent use.

(3) If you use wet processing during manufacturing, you must clean and sanitize all contact surfaces, as necessary, to

protect against the introduction of microorganisms into components, dietary ingredients, or dietary supplements. When cleaning and sanitizing is necessary, you must clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may have become contaminated. If you use contact surfaces in a continuous production operation or in back-to-back operations involving different batches of the same dietary ingredient or dietary supplement, you must clean and sanitize the contact surfaces as necessary.

(4) You must clean surfaces that do not touch components, dietary ingredients, or dietary supplements as frequently as necessary to protect against contaminating components, dietary ingredients, or dietary supplements.

(5) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) must be:

(i) Stored in appropriate containers; and

(ii) Handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or any contact surface.

(6) Cleaning compounds and sanitizing agents must be adequate for intended use and safe under condition of use;

(7) You must store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and manner that protects them from contamination.

(f) You must keep calibration records as required by this section in accordance with § 111.125.

§ 111.30 What requirements apply to automatic, mechanical, or electronic equipment?

(a) When you use automatic, mechanical, or electronic equipment to manufacture, package, label, and hold a dietary ingredient or dietary supplement, you must:

(1) Design or select equipment to ensure that dietary ingredient or dietary supplement specifications are consistently achieved and

(2) Determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process.

(b) For any automatic, mechanical, or electronic equipment you use, you must:

(1) Routinely calibrate, inspect, or check to ensure proper performance. Your quality control unit must approve these calibrations, inspections, or checks;

(2) Make and keep written records of equipment calibrations, inspections, or checks;

(3) Establish and use appropriate controls, to ensure that your quality control unit approves changes in the master manufacturing record, batch control records, packaging operations and label operations, or changes to other operations related to

the equipment that you use and that only authorized personnel institute the changes;

(4) Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. These controls must be approved by your quality control unit; and

(5) Make and keep backup file(s) of software programs and of data entered into your computer system. Your backup file (e.g., a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered. You must keep your backup software programs and data secure from alterations, inadvertent erasures, or loss.

(c) You must keep automatic, mechanical, or electronic equipment records required by this section in accordance with § 111.125.

§ 111.50 [Redesignated as § 111.72 and Amended]

7. Redesignate § 111.50 as § 111.72 and transfer it to a new subpart E, Production and Process Controls, and revise the section heading to read as follows:

§ 111.72 What requirements apply to packaging of iron-containing dietary supplements?

* * * * *

8. Add §§ 111.35 through 111.70 and § 111.74 to newly added subpart E to read as follows:

§ 111.35 What production and process controls must you use?

(a) You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary ingredients and dietary supplements.

(b) Your production and in-process control system must be designed to ensure that the dietary ingredient or dietary supplement is manufactured, packaged, and held in a manner that will prevent adulteration of the dietary ingredient or dietary supplement. The production and in-process control system must include all requirements of this subpart and must be reviewed and approved by the quality control unit.

(c) You must use a quality control unit in your manufacturing, packaging, and label operations for producing the dietary ingredient or dietary supplement to ensure that these operations are performed in a manner that prevents adulteration and ensures that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.

(d) Any substance, other than a "dietary ingredient" within the meaning of section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the act), the intended use of which results or may reasonably be expected to result, directly or indirectly, in its

becoming a component or otherwise affecting the characteristics of the dietary ingredient or dietary supplement must be:

(1) Authorized for use as a food additive under section 409 of the act; or

(2) Authorized by a prior sanction consistent with § 170.3(l) of this chapter; or

(3) If used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement; or

(4) Generally recognized as safe (GRAS) for use in a dietary ingredient or dietary supplement. Any claim that a substance is GRAS, other than a dietary ingredient within the meaning of section 201(ff) of the act, must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement; and

(5) Must comply with all other applicable statutory and regulatory requirements under the act.

(e) You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration. Specifications must be established for:

(1) The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive;

(2) The in-process controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements;

(3) The identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement that you manufacture; and

(4) The dietary ingredient or dietary supplement labels and the packaging that may come in contact with dietary ingredients and dietary supplements. The packaging must be safe and suitable for its intended use and comply with all other applicable statutory and regulatory requirements under the act and must not be reactive or absorptive so as to affect the safety of the dietary ingredient and dietary supplement.

(f) You must monitor the in-process control points, steps, or stages to ensure that specifications established under paragraph (e) of this section are met and to detect any unanticipated occurrence that may result in adulteration;

(g) You must ensure, through testing or examination, that each specification that you established under paragraph (e) of this section is met. Specific testing requirements are as follows:

(1) You must test each finished batch of the dietary ingredient or dietary supplement produced before releasing for

distribution to determine whether established specifications for identity, purity, quality, strength, and composition are met, provided that there are scientifically valid analytical methods available to conduct such testing.

(2) For any specification for identity, purity, quality, strength, or composition for which you document cannot be tested on the finished batch of a dietary ingredient or dietary supplement, because there is no scientifically valid analytical method available for such testing, then you must:

(i) Perform testing on each shipment lot of components, dietary ingredients or dietary supplements received to determine whether such specification is met; and

(ii) Perform testing in-process in accordance with the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements; and

(3) Your quality control unit must determine when finished batch testing cannot be completed for any specification on the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements.

(h) You must use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that is a scientifically valid analytical method.

(i) You must:

(1) Establish corrective action plans for use when an established specification is not met;

(2) Review the results of the monitoring required by this section and conduct a material review of any component, dietary ingredient, dietary supplement, packaging or label for which you establish a specification that is not met, or any unanticipated occurrence that adulterates or could result in adulteration of the component, dietary ingredient, dietary supplement, packaging, or label; and

(3) Make a material disposition decision for any component, dietary ingredient, dietary supplement, packaging, or label:

(i) If a component, dietary ingredient, dietary supplement, packaging, or label fails to meet specifications;

(ii) If any step established in the master manufacturing record is not completed;

(iii) If there is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label;

(iv) If calibration of an instrument or control suggests a problem that may have caused batches of a dietary ingredient or dietary supplement to become adulterated; or

(v) If a dietary ingredient or dietary supplement is returned.

(4) Have your quality control unit review and approve any material review and disposition decision described in paragraphs (i)(2) and (i)(3) of this section.

(j) The person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in paragraph (i) of this section. The documentation must be included in the appropriate batch production record and must:

(1) Identify the specific deviation from the specification or the unanticipated occurrence;

(2) Describe your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

(3) Evaluate whether or not the deviation from the specification or unanticipated occurrence has resulted in or could lead to adulteration. For any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, you must reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence. You must not reprocess a rejected component, dietary ingredient, or dietary supplement unless approved by the quality control unit. You must not reprocess any component, dietary ingredient or dietary supplement if it is

rejected because of contamination with microorganisms or other contaminants, such as heavy metals;

(4) Identify the action(s) taken to correct and prevent a recurrence of the deviation or the unanticipated occurrence;

(5) Discuss what you did with the component, dietary ingredient, dietary supplement, packaging, or label; and

(6) Show that your quality control unit approved the material disposition decision.

(k) You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following:

(1) Filth, insects, or other extraneous material;

(2) Microorganisms; and

(3) Toxic substances.

(l) Tests in accordance with this section must include at least one of the following:

(1) Gross organoleptic analysis;

(2) Microscopic analysis;

(3) Chemical analysis; or

(4) Other appropriate test.

(m) You must record results of all testing and examinations

performed in accordance with this section. Your records must document whether the testing and examination demonstrates that specifications are met.

(n) For any specification that is not met, you must conduct a material review and disposition decision under paragraph (i) of this section.

(o) You must make and retain records, in accordance with § 111.125, to ensure that you follow the requirements of this section. The records must include, but are not limited to:

(1) The specifications established;

(2) The actual results obtained during the monitoring operation;

(3) Any deviation from specifications and any unanticipated occurrences;

(4) Any corrective actions taken;

(5) The disposition decisions and followup; and

(6) The identity of the individual qualified by training and experience who investigated any deviation from specifications or unanticipated occurrence and the identity of the individual from the quality control unit who reviewed the results of that investigation.

§ 111.37 What requirements apply to quality control?

(a) You must use a quality control unit to ensure that your manufacturing, packaging, label, and holding operations in the

production of dietary ingredients and dietary supplements are performed in a manner that prevents adulteration and misbranding, including ensuring that dietary ingredients and dietary supplements meet specifications for identity, purity, quality, strength, and composition.

(b) Your quality control unit must do the following:

(1) Approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, quality, strength, and composition of a dietary ingredient or dietary supplement;

(2) Determine whether all components, dietary ingredients, dietary supplements, packaging, and labels conform to specifications;

(3) Approve or reject all components, dietary ingredients, dietary supplements, packaging, and labels;

(4) Review and approve all master manufacturing records and all modifications to the master manufacturing records;

(5) Review and approve all batch production-related records which include, but are not limited to, cross referencing receiving and batch production records, approval of a material review and disposition decision, approval for reprocessing, and approval for releasing for distribution;

(6) Review and approve all processes for calibrating

instruments or controls;

(7) Review all records for calibration of instruments, apparatus, gauges, and recording devices;

(8) Review all records for equipment calibrations, inspections, and checks;

(9) Review and approve all laboratory control processes, and testing results;

(10) Review and approve all packaging and label records which include, but are not limited to, cross-referencing receiving and batch production records, approval for repackaging and relabeling, and approval for releasing for distribution;

(11) Collect representative samples of:

(i) Each shipment lot of components, dietary ingredients, dietary supplements, packaging, and labels received to determine whether the component, dietary ingredient, dietary supplement, packaging, or labels meet specifications;

(ii) Inprocess materials at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements;

(iii) Each batch of dietary ingredient or dietary supplement manufactured to determine, before releasing for distribution, whether the dietary ingredient or dietary supplement meets its

specifications for identity, purity, quality, strength, and composition; and

(iv) Each batch of packaged and labeled dietary ingredients or dietary supplements to determine that you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record.

(12) Keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. The reserve samples must:

(i) Be identified with the batch or lot number; and

(ii) Consist of at least twice the quantity necessary for tests.

(13) Perform appropriate tests and examinations of:

(i) Components, dietary ingredients, dietary supplements, packaging, and labels received to ensure that they meet specifications;

(ii) Dietary ingredient and dietary supplement batch production at points, steps, or stages identified in the master manufacturing record where control is necessary to prevent adulteration;

(iii) Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and

(iv) Packaged and labeled dietary ingredients and dietary supplements to ensure that you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record.

(14) Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.

(c) Your quality control unit must establish and maintain written documentation at the time of performance that it met the requirements of this section by recording the following:

(1) Date the requirement was performed;

(2) Signature of the person performing the requirement; and

(3) Results of any test and examination performed.

(d) You must keep quality control records in accordance with § 111.125.

§ 111.40 What requirements apply to components, dietary ingredients, dietary supplements, packaging, and labels you receive?

(a) For components, dietary ingredients, or dietary supplements you receive, you must:

(1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container

condition has resulted in contamination or deterioration of the components, dietary ingredients, or dietary supplement;

(2) Visually examine the suppliers invoice, guarantee, or certification to ensure that the components, dietary ingredients, or dietary supplements are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met.

(3) Quarantine components, dietary ingredients, or dietary supplements until your quality control unit reviews the suppliers invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that specifications are met. If specifications are not met, you must conduct a material review and make a disposition decision. Your quality control unit must approve and release the components, dietary ingredients, and dietary supplements from quarantine before you use them;

(4) Identify each lot of components, dietary ingredients, or dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component or dietary supplement, and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique identifier whenever you record the disposition of each shipment

lot received; and

(5) Hold components, dietary ingredients, or dietary supplements under conditions that will protect against contamination, deterioration, and avoid mixups.

(b) For packaging and labels you receive, you must:

(1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition has resulted in contamination or deterioration of the packaging and labels;

(2) Quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met. You must conduct at least a visual identification on the containers and closures. If specifications are not met, you must conduct a material review and make a disposition decision. Your quality control unit must approve and release packaging and labels from quarantine before you use them;

(3) Identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique

identifier whenever you record the disposition of each shipment lot received; and

(4) Hold packaging and labels under conditions that will protect against contamination, deterioration, and avoid mixups.

(c)(1) The person who performs the component, dietary ingredient, dietary supplement, packaging, or label requirements of this section must document, at the time of performance, that the requirements were followed. The documentation must include, but not be limited to:

(i) The date that the components, dietary ingredients, dietary supplements, packaging, or labels were received;

(ii) The signature of the person performing the requirement;

(iii) Any test results; and

(iv) Any material review and disposition decision you conducted in accordance with § 111.35(i) and disposition of any rejected material under § 111.74.

(2) You must keep component, dietary supplement, packaging, and label receiving records in accordance with § 111.125.

§ 111.45 What requirements apply to establishing a master manufacturing record?

(a) You must prepare and follow a written master manufacturing record for each type of dietary ingredient or dietary supplement that you manufacture and for each batch size

to ensure uniformity from batch to batch. The master manufacturing record must:

(1) Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration; and

(2) Establish controls and procedures to ensure that each batch of dietary ingredient or dietary supplement manufactured meets those specifications.

(b) The master manufacturing record must include the following information:

(1) The name of the dietary ingredient or dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;

(2) A complete list of components to be used;

(3) An accurate statement of the weight or measure of each component to be used;

(4) The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement in compliance with section 403(s) of the Federal Food, Drug, and Cosmetic Act;

(5) A statement that explains any intentional excess amount of a dietary ingredient;